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Offline Bi-Frontal Anodal Transcranial Direct Current Stimulation Decreases Total Sleep Time Without Disturbing Overnight Memory Consolidation

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Objectives: A proposed replay of memory traces between the hippocampus and frontal cortical brain areas during sleep is of high relevance for overnight memory consolidation. Recently, we demonstrated that bi-frontal anodal transcranial direct current stimulation (tDCS) prior to sleep increases waking EEG gamma power and decreases total sleep time during the night. It is unclear whether this effect on cortical excitability has an influence on overnight memory consolidation. We hypothesized that bi-frontal evening tDCS interferes with overnight memory consolidation with a polarity specific impairment following anodal tDCS.

Materials and Methods: Nineteen healthy participants underwent a within-subject, repeated-measures protocol in the sleep laboratory with bi-frontal tDCS applied prior to sleep according to the experimental protocol (anodal, cathodal, sham stimulation). Memory tasks for declarative and procedural memory were assessed prior to tDCS and on the following morning.

Results: No deterioration of overnight memory consolidation following evening offline bi-frontal tDCS could be detected.

Conclusion(s): The application of tDCS can be considered safe regarding overnight memory consolidation and represents a promising treatment approach in conditions of decreased vigilance and arousal.

Keywords: Adverse events, EEG, learning, side effects, sleep, transcranial direct current stimulation (tDCS)

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INTRODUCTION

Identification of neural mechanisms underlying learning and novel ways to improve them has been an important research topic for decades. To date, sleep represents one of the most discussed influence factors on memory consolidation. A proposed hippocampal–cortical replay of memory traces during sleep is conceptualized to gradually strengthen memory representations (1). Presumably, effects are mediated through an interaction of strengthening of relevant synapses by active neuronal replay of memory representations and sharpening of representations through downselection of non-relevant synapses (2). Non rapid eye movement sleep (NREM) EEG characteristics, such as slow oscillations, spindles, and thalamic ripples are conceptualized to orchestrate this process (3–5).

Noninvasive brain stimulation techniques such as transcranial direct current stimulation (tDCS) have been introduced as a tool to modulate neural integration of memory representations (6). Usage of slow electrical waveforms produced by transcranial electric devices (slow oscillating tDCS, so-tDCS; transcranial alternating current stimulation, tACS) has been demonstrated to be capable of entraining endogenous slow oscillations and boosting slow

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wave sleep (7). By influencing slow oscillations, improvement (8,9) as well as deterioration (10) of overnight memory consolidation has been described, depending on the specific stimulation parameters.

In contrast, traditional tDCS induces stable electric field changes in broad areas underlying the stimulation electrodes. The rationale states excitability increasing, respectively decreasing effects on neural networks depending on the polarity of the target electrodes, and directionality of the induced electric field. These excitability changes then influence intrinsic generation of brain oscillations and activity levels of cortico-subcortical connections indirectly (11). Beyond these effects, tDCS induces polarity-specific plasticity relevant for learning processes (12,13).

Recently, we demonstrated that bi-frontal anodal tDCS immediately prior to sleep enhances cortical excitability thereby decreasing total sleep time (TST) during the following night (14). It remained unclear whether this sleep disruption has an influence on overnight sleep related memory consolidation. While no specific sleep characteristics linked to memory consolidation, such as sleep EEG slow wave activity, appeared altered, the profound effect of tDCS on TST (14) might still influence cognitive functioning. In a group of insomnia disorder patients, shorter sleep duration was associated with poorer cognitive performance (15).

The current study analyses declarative and procedural memory consolidation that were conducted prior to offline tDCS and the following morning. We hypothesized that both sleep-related declarative and procedural memory consolidation will be impaired due to a stimulation-induced decrease in total sleep time.

MATERIALS AND METHODS

Study Design

The analyses of the current work were conducted as part of a larger examination of tDCS effects on sleep and sleep related processes (14,16). All participants underwent a within-subject, repeated-measures protocol across three nights in the sleep laboratory with tDCS applied according to the experimental protocol (anodal, cathodal, and sham stimulation) at 10:00 PM prior to polysomnographic recorded sleep from 11:00 PM to 07:00 AM (Fig. 1a). Experimental protocols were alternated in a counterbalanced order to exclude sequence effects and were separated by one week to prevent carry-over effects. Stimulation induced effects on sleep and resting state wake EEG have been previously published (14).

Two tasks that have repeatedly been demonstrated to involve sleep-related memory consolidation, the declarative memory task "paired-associate word list" (WL) (17) and the procedural memory task "fingertapping" (FT) (18) were assessed prior to tDCS and on the following morning after polysomnography. To allow repeated testing, three parallel versions of the tasks were presented to the participants in a counterbalanced order across experimental nights. To control for unspecific cognitive effects of tDCS, a standardized test for attentional performance (TAP, subtest for tonic or phasic alertness (19)) was conducted prior to each learning and recall session.

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the University Medical Center Freiburg (271/12-130471). The study was registered in the German Register for Clinical Studies (www.germanctr.de, DRKS00004299).

Participants

Nineteen healthy participants (13 females, 6 males, age 53.7 $\pm$ 6.9 years, age range 40–65 years) were included in the study. Due to technical difficulties, three participants did not complete FT, while one participant did not complete WL, leading to a subset of 16 (FT), respectively 18 (WL) participants in the final analysis. All participants underwent an extensive screening, as described previously (14) to rule out any relevant mental, physical or sleep disorder, or any tDCS-specific exclusion criteria (20). All participants were right handed, nonsmokers, and did not consume any caffeine, alcohol, or medication during the study. Prior to study inclusion, all participants provided written informed consent.

Learning and Memory Assessment

Procedural memory was assessed by using a standard fingertapping task (FT) (18), with the software provided by Rasch (21). In this task, participants are instructed to type a specific five digit sequence as fast and correct as possible. The target sequence was displayed on a standard personal computer monitor. Neither a maximum amount of target sequences per trial nor a time limit to respond to a specific target sequence was determined. After a brief instruction and explanatory test session, twelve 30 sec trials separated by 30 sec interstimulus intervals were completed prior to tDCS in the evening (training session) and on the next morning (retrieval session). The number of correctly completed sequences per trial was defined as the main outcome parameter to represent a combined measure of speed and accuracy. This parameter was averaged over the last three trials of the training session ("learning"), the first three trials of the morning retrieval session ("early retrieval") and the last three trials of the morning retrieval session ("late retrieval"). In addition, overnight performance change was examined by computing the difference between learning and early retrieval and performance gain during the morning retrieval session was defined as the difference between early and late retrieval (22).

Declarative memory was assessed by using a paired-associate word list (7). During the learning phase, 44 word pairs are presented in randomized order for 5 sec each. Participants are instructed to remember the corresponding word pairs. Afterwards, only the first word of each pair is presented for a maximum duration of 30 sec and participants are asked to name the corresponding word. If participants remember less than 24 word pairs (60%) correctly, another learning trial is completed (maximum five trials). During retrieval, only one round of single word presentation is presented. The percentage of correctly remembered word pairs during retrieval in relation to correctly encoded word pairs during learning was defined as the main outcome parameter. To diminish potential primacy or recency effects, the first two as well as the last two word pairs were excluded from the analysis.

Transcranial Direct Current Stimulation

tDCS was delivered as described in a previous publication using the same study sample (14). In short, tDCS was delivered by bi-frontal target electrodes (5 $\times$ 7 cm, FP1/FP2) and bi-parietal return electrodes (10 $\times$ 10 cm, P3/P4) covered with electrode cream

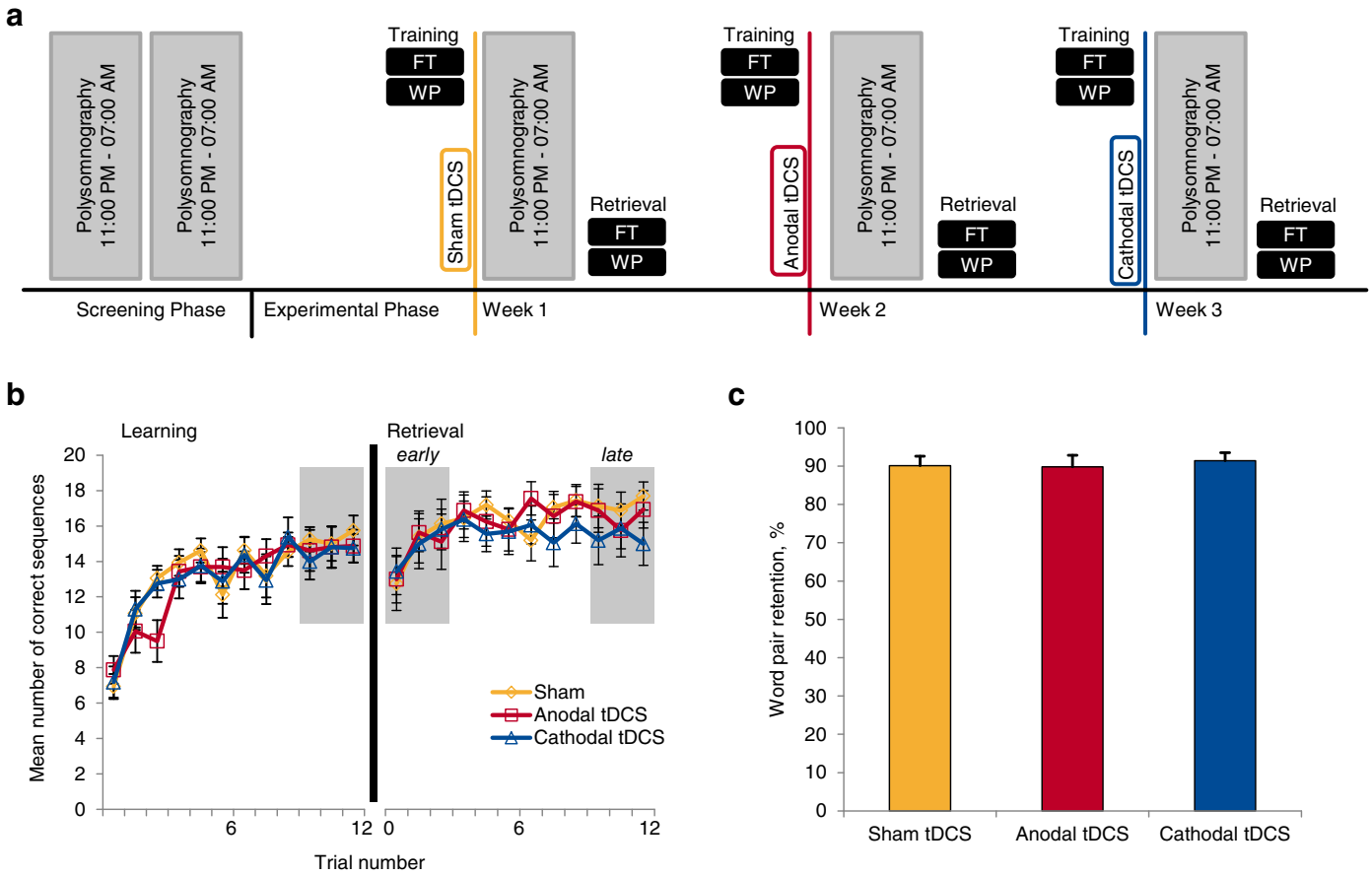

Figure 1. a. Study design. After a thorough screening phase including two nights of polysomnography, participants concluded three counterbalanced experimental sessions separated by one week in a within-subject, repeated-measures protocol. Transcranial direct current stimulation (tDCS) according to the experimental protocol (anodal, cathodal, and sham stimulation) was applied at 10:00 PM prior to polysomnographic recorded sleep from 11:00 PM to 07:00 AM. The declarative memory task "paired-associate word list" and the procedural memory task "fingertapping" were assessed prior to tDCS and on the following morning after polysomnography. b. tDCS effects on procedural memory. Means of correct sequences are displayed for each trial during learning and retrieval. No baseline differences between conditions (sham tDCS, yellow diamond; anodal tDCS, red square; cathodal tDCS, blue triangle) were detected for the learning phase. Against our hypothesis, no diminishing effects of anodal tDCS on either sleep-related memory consolidation or post-sleep on task performance were detected. Trials included in the main analysis are highlighted by a gray background. Means +/− SEM. c. tDCS effects on declarative memory. Percentage of word pair retention during retrieval compared to learning. No differences between conditions (sham tDCS, yellow; anodal tDCS, red; cathodal tDCS, blue) were detected in both stages of the experimental sessions. Means +/− SEM. [Color figure can be viewed at wileyonlinelibrary.com]

(Ten20 Conductive EEG Paste, Weaver, Aurora, CO, USA). A constant current of 1 mA over each electrode was applied (2 mA stimulator output, Y-cable split) with a 30 sec fade-in/fade-out design to reduce potential skin reactions. To induce prolonged after-effects on neural plasticity and memory, optimized repetitive stimulation protocols were employed for each condition (2 × 13 min anodal tDCS, 2 × 9 min cathodal tDCS with 20 min inter-stimulation intervals (23,24)). Participants were blinded for and were not able to discern between the tDCS conditions (14).

Polysomnography

Polysomnography was recorded from 11:00 PM to 07:00 AM according to standard procedures (14) and recordings were visually scored off-line by experienced raters according to the American Academy of Sleep Medicine criteria (25). NREM EEG characteristic electrophysiological shapes (graphoelements), such as slow oscillations, spindles and thalamic ripples, are narrowly defined frequencies within NREM sleep that can be quantitatively analyzed using spectral analysis. We have therefore performed spectral power analysis in NREM sleep to assess power spectra for delta 0.1–3.5 Hz (delta 1 0.1–1.5 Hz; delta 2 1.5–3.5 Hz); theta 3.5–8 Hz; alpha 8–12 Hz; sigma 12–16 Hz (sigma 1 12–14 Hz; sigma 2 14–16 Hz); beta 16–24 Hz (beta 1 16–20 Hz, beta 2 20–24 Hz); and gamma 24–50 Hz as previously described in detail (14,26).

Statistical Analyses

Descriptive values are given as means and standard deviations. To test for memory differences, repeated measures analyses of variance (ANOVAs) with the within subject factor Condition (anodal stimulation, cathodal stimulation, and sham stimulation) were conducted. Overnight performance change in FT as well as overnight WP retention was used as the primary outcome parameters. Power calculation was done for this analysis (*F* test with repeated measures, G*Power 3.1.9.2). Other analyses were secondary analyses. For the estimation of effect sizes, partial ETA square (η^2_p) values were calculated (low: <.06; medium: ⩾.06; and < .14; large: ⩾.14). The level of significance was set at $p = .05$ (two-

Table 1. Effects of Transcranial Direct Current Stimulation on Overnight Memory Consolidation.

	Sham tDCS	Anodal tDCS	Cathodal tDCS	*F*	*p*	$pETA^2$
Procedural memory—Fingertapping task						
Learning, correct sequences	15.4 ± 3.0	14.8 ± 4.0	14.5 ± 3.5	.4	.660	.024
Early retrieval, correct sequences	14.8 ± 4.7	14.6 ± 4.7	14.8 ± 4.7	<.1	.955	.001
Overnight change, %	−3.3 ± 25.1	3.1 ± 31.4	.9 ± 14.9	.3	.723	.019
Late retrieval, correct sequences	17.2 ± 3.7	16.5 ± 4.2	15.4 ± 4.4	2.4	.146	.136
Late retrieval, on-task performance change, %	25.1 ± 38.9	17.4 ± 28.3	5.4 ± 19.9	1.7	.209	.100
Declarative memory—Paired-associate word list task						
Learning, correct word pairs	30.8 ± 4.1	30.1 ± 4.0	30.3 ± 4.5	.2	.811	.012
Learning, trials needed	1.8 ± 0.8	1.9 ± 0.9	1.9 ± 0.9	.3	.751	.017
Correct word pair retention, %	90.1 ± 10.5	89.8 ± 12.9	91.4 ± 8.7	.2	.820	.012

Neither bi-frontal anodal nor cathodal transcranial direct current stimulation modulated memory performance in a procedural fingertapping task or a declarative paired-associate word list task. In addition, no baseline (learning) differences between intervention conditions could be detected. Means ± SDs. ANOVAs with the within-subject factor Condition (sham, anodal, cathodal stimulation). $pETA^2$, partial eta square.

tailed). All analyses were conducted with the statistical software IBM SPSS Statistics, version 21 (IBM Co., Armonk, NY, USA).

RESULTS

Against our primary hypothesis, no diminishing effects of anodal tDCS on consolidation parameters of neither procedural memory, examined using the FT, nor declarative memory, using the paired-associate word list task (WL), were detected (Fig. 1b,c; Table 1). As FT late retrieval parameters displayed medium to large effect sizes, we conducted post-hoc power analyses demonstrating sufficient power levels for the null hypothesis (Late retrieval, correct sequences: $1-\beta = .92$; Late retrieval, on-task performance change, %: $1-\beta = .80$).

In addition, no baseline differences between conditions were found during the learning phase (Table 1). To detect initial retrieval differences without subsequent training gains, we analyzed the difference between training and the first trial of the morning retrieval session. No significant stimulation effects could be detected ($F = 0.6$; $p = .540$; $pETA^2 = .037$).

To further explore potential interferences between sleep architecture and memory consolidation, exploratory correlation analyses were conducted. As reported by Frase et al., participants included in the current analysis displayed a polarity and location specific decrease of TST following anodal stimulation (387.4 ± 44.5 min) compared to sham stimulation (412.6 ± 27.7 min; F = 5.5; $p = .017$; $pETA^2 = .235$) (14).

No consistent interaction between stimulation, memory and sleep stages as well as sleep EEG spectral power bands could be detected besides a minor association between delta 1 EEG

Table 2. Effects of NREM Sleep EEG Spectral Power in Different Stimulation Conditions on Overnight Memory Consolidation.

		Procedural memory—Fingertapping task Overnight change in correct results, %			Declarative memory—Paired-associate word list task Correct word pair retention, %		
		Sham tDCS	Anodal tDCS	Cathodal tDCS	Sham tDCS	Anodal tDCS	Cathodal tDCS
Delta 1	PCC	.219	−.024	−.241	.269	.361	.490
	p	.382	.924	.336	.281	.141	**.039**
Delta 2	PCC	.317	−.074	−.277	.189	.280	.300
	p	.199	.772	.266	.454	.260	.226
Theta	PCC	.260	.096	−.212	.079	.116	.097
	p	.297	.705	.397	.755	.648	.703
Alpha	PCC	.011	.301	−.103	−.065	.018	−.025
	p	.965	.225	.685	.798	.945	.922
Sigma 1	PCC	.070	−.016	−.013	.226	.313	.234
	p	.784	.950	.958	.367	.205	.350
Sigma 2	PCC	.264	−.159	−.170	.321	.213	.385
	p	.289	.529	.501	.194	.397	.115
Beta 1	PCC	.036	.017	.044	−.012	.024	−.193
	p	.888	.945	.861	.962	.925	.443
Beta 2	PCC	.003	−.139	−.434	.143	.034	.114
	p	.992	.584	.072	.572	.893	.651
Gamma	PCC	.085	−.064	−.035	.080	.013	−.176
	p	.737	.802	.892	.753	.960	.486

Note: The bold value shown significant *p*-value.
No correlation between sleep EEG spectral power and overnight memory correlation could be detected besides a slight uncorrected correlation between Delta1 EEG spectral power and cathodal tDCS. PCC, Pearson correlation coefficient.

spectral power and cathodal tDCS (Pearson correlation coefficient = .490, $p = .039$ [uncorrected], all other $p > .05$; Table 2). To fully explore potential effects of NREM sleep EEG delta and sigma power, as the most relevant power spectra for memory consolidation, on overnight memory consolidation we then reanalyzed the data using differences in EEG spectral power parameters between sham and active stimulation and differences in the main memory outcome parameters between sham and active stimulation. No significant correlations could be detected (all $p > .05$; see Table S1, supplements).

To control for known potential confounders of memory assessment, participants were carefully screened and reported predominantly higher education as well as regular employment with mean weekly work duration of 31.6 $\pm$ 12.5 hours. Intelligence as assessed by Raven's Standard Progressive Matrices (27) showed average intelligence quotient levels (101.5 $\pm$ 12.5). Changes in tonic or phasic attention levels were controlled by using a standardized TAP (19). No general differences in attentional performances between conditions were detected, as described earlier by Frase et al. (16). To further explore potential effects of other relevant parameters were conducted. No interactions between stimulation, memory and IQ as well as attentional performance could be detected (all $p > .05$, data not shown). To further investigate effects on continuous on-task performance, FT performance during late retrieval was analyzed. No significant differences between stimulation conditions were detected and performance gains displayed expected levels ((22), Table 1).

DISCUSSION

In summary, we demonstrated no influence of bi-frontal anodal offline tDCS on following overnight declarative or procedural memory consolidation. As described in Frase et al. (14), bi-frontal anodal stimulation decreased TST in the following night by about 25 min. While this effect was polarity and stimulation location specific and led to persisting wake EEG differences on the next morning immediately prior to memory assessment (14), no corresponding effects were observed in the current analyses of sleep related memory processes.

Our results add to the growing body of evidence for the importance of timing when using tDCS to influence memory tasks. While positive effects of concurrent (online) tDCS on encoding are better examined and established (6), offline effects of tDCS on memory consolidation following stimulation are more controversial. Nitsche et al. demonstrated that tDCS conducted over premotor areas during REM sleep improves recall of procedural memory information (28). tDCS during the interval between learning and sleep during the afternoon did not influence consolidation processes (28). A recent meta-analysis concluded that declarative memory consolidation could be enhanced by tDCS during NREM, but that, in summary, evidence for modulation of procedural memory is lacking (29). Reis et al. described improved long-time consolidation effects on procedural memory following tDCS during learning/encoding compared to sham that were dependent on time to follow-up, but not on sleep. Again, tDCS after the learning phase did not influence consolidation (30). In concordance with the current results, the literature supports the hypothesis, that direct tDCS effects can only be found if stimulation is administered online either during learning/encoding or (sleep related) consolidation processes (online), but not if conducted in an interval between those (offline). As a potential limitation, it is to note that the analyses could be interpreted to show a nonsignificant superiority of sham compared to active tDCS with medium effect sizes regarding late retrieval gains in the FT. It can be speculated whether a larger sample size would have been able to detect significant tDCS effects on procedural memory.

The overall lacking effect on sleep related processes such as memory consolidation stands in contrast to the capability of decreasing the amount of nocturnal sleep following offline tDCS (14). We recently provided preliminary evidence that the same tDCS protocol as applied in this study was capable of improving vigilance and reducing daytime sleepiness in a patient with organic hypersomnia following reanimation (31). The application of bi-frontal tDCS in conditions of decreased vigilance and arousal as a potential inpatient or even home treatment is promising regarding the very limited treatment options for such conditions (11).

CONCLUSION

The current findings add to the evaluation of tDCS as a safe technique. This might encourage further research projects in this area and strengthens the availability of tDCS as a potential treatment option for patients with pathologically increased sleep and decreased vigilance.

Authorship Statement

Lukas Frase, Hannah Piosczyk, Dieter Riemann, Michael A. Nitsche, and Christoph Nissen designed the study. Lukas Frase, Friederike Jahn, Sulamith Tsodor, Lukas Krone, and Peter Selhausen did patient recruitment and data collection. Lukas Frase, Friederike Jahn, Bernd Feige, Jonathan G. Maier, and Christoph Nissen were responsible for the main data analysis. Lukas Frase and Christoph Nissen prepared the manuscript draft with important intellectual input from all authors. All authors approved the final manuscript.

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SUPPORTING INFORMATION

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